HHS Public Access

Author manuscript

J Clin Pharmacol. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

J Clin Pharmacol. 2015 May ; 55(5): 556–562. doi:10.1002/jcph.449.

Clinical Trial Simulation to Evaluate Population Pharmacokinetics and Food Effect: Capturing Abiraterone and Nilotinib Exposures

Claire H. Li, PhD[1,2], **Eric A. Sherer, PhD**[1,2,3], **Lionel D. Lewis, MB BCh, MD**[4], and **Robert R. Bies, PharmD, PhD**[1,2]

[1]Indiana University School of Medicine, Indianapolis, IN, USA

[2]Indiana Clinical and Translational Sciences Institute (CTSI), Indianapolis, IN, USA

[3]Louisiana Tech University, Ruston, LA, USA

[4] Section of Clinical Pharmacology, Department of Medicine, The Geisel School of Medicine at Dartmouth & Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Abstract

The objectives of this study were to determine (1) the accuracy with which individual patient level exposure can be determined and (2) whether a known food effect can be identified in a trial simulation of a typical population pharmacokinetic trial. Clinical trial simulations were undertaken using NONMEM VII to assess a typical oncology pharmacokinetic trial design. Nine virtual trials for each compound were performed for combinations of different level of between-occasion variability, number of patients in the trial and magnitude of a food covariate on oral clearance. Less than 5% and 20% bias and precision were obtained in individual clearance estimated for both abiraterone and nilotinib using this design. This design resulted biased and imprecise population clearance estimates for abiraterone. The between-occasion variability in most trials was captured with less than 30% of percent bias and precision. The food effect was detectable as a statistically significant covariate on oral clearance for abiraterone and nilotinib with percent bias and precision of the food covariate less than 20%. These results demonstrate that clinical trial simulation can be used to explore the ability of specific trial designs to evaluate the power to identify individual and population level exposures,covariate and variability effects.

Keywords

Abiraterone; Nilotinib; Population pharmacokinetics; Clinical Trial simulation

Correspondence to: Claire H. Li.

Address for correspondence: Robert R. Bies, Division of Clinical Pharmacology, Research Institute (R2), Room 402, 950 West Walnut Street, Indianapolis IN 46202, Phone: 317-274-2822, Fax: 317-274-2704, rrbies@iu.edu.

INTRODUCTION

In the past twenty years, oral anticancer drug therapy has become more prevalent [1]. Unlike intravenous drug administration, orally administered agents undergo absorption from the gastrointestinal lumen through the intestinal epithelium into the portal vein and then into the systemic circulation. The fraction of an orally administered drug dose that reaches the systemic circulation is the drug's oral bioavailability. Significant changes in bioavailability will lead to a significant change in drug exposure [2] and thus modified therapeutic and/or toxic effects.

One of the most common factors contributing to changes in oral bioavailability is food intake [1, 3-4]. The effect of food on oral bioavailability has the potential to cause a clinically significant impact on systemic drug exposures that can lead to drug toxicity and/or therapeutic failure [5-6]. Furthermore, the alteration of pharmacokinetic profile of several standard and investigational anticancer drugs such as busulfan, topotecan and fluorouracil caused by food-drug interactions have been previously reported [1]. Quantifying the effect of food on drug exposure is, therefore, important when designing a clinical trial for oral anti-cancer drugs. Additionally, variability between individuals as well as between occasions also contributes to variability in drug response. In order to assess the contribution of different magnitudes of between-individual and between-occasion variability on drug exposure, this study used a population PK modeling approach and Monte Carlo methods to simulate a virtual clinical trial of patients who took drug in both the fasted and fed states.

Such a clinical trial simulation framework provides insight as to whether a particular study design, with a random sampling schema to reflect a typical clinical practice setting, permits the retrieval of pharmacokinetic (PK) parameters and their variability under different prandial conditions. In addition, simulation of a clinical trial can assess how patient specific covariates, between-individual, and between-occasion variability affect the ability to accurately capture individual level exposures. The aim of this study was to evaluate whether a pre-defined oncology trial with a sparse drug concentration sampling schedule can adequately capture individual level drug exposures, random variability and the food effects of two recently approved drugs, abiraterone and nilotinib. To achieve these objectives, a virtual cancer study population was simulated with assigned pharmacokinetic characteristics, food intake and between-individual as well as between-occasion variability. A population pharmacokinetic (Pop PK) approach was utilized to retrieve the Pop PK parameters under these conditions and examine whether or not these parameters could be adequately retrieved on estimation at both the individual and population level.

MATERIALS AND METHODS

Simulation of Patient Pharmacokinetic Characteristics

Hypothetical patients were created with fasting state Pop PK parameters mimicking those found in oncology patients. (See Table 1 for abiraterone [7] and Table 2 for nilotinib [8-9] patient characteristics). The Pop PK parameters were assumed to be log normally distributed and the parameter values for simulation were obtained or calculated based on literature values from a noncompartmental analyses [7-9]. A one compartment model with first order

absorption and elimination was assumed as the model structure. Between-individual variability of oral clearance (CL/F) and volume of distribution (Vd/F) were based on the mean and standard deviation of pharmacokinetic parameters from the above published studies. Abiraterone between-individual variability values for oral clearance and volume of distribution were 174% and 73%, respectively, in the fasted state and 42.2% and 36%, respectively, in the fed state [7]. The between-individual variability of the absorption rate constant was assumed to be 20% and a proportional residual error with 30% coefficient of variation (CV) was assumed based on literature values for abiraterone [7]. For nilotinib, the between-individual variability of oral clearance and volume of distribution values were set to 55% and 37% CV, respectively, for both fed and fasting states [9]. A between-individual variability for the nilotinib absorption rate constant of 20% and a proportional residual error with 10% CV based on the lower limit of quantification of the nilotinib concentration assay were assumed [9].

Values of the Pop PK parameters for each hypothetical patient were randomly chosen from their respective distributions with a correlation of 0.6 applied between clearance and volume of distribution.

Food effects

For both abiraterone and nilotinib, it was assumed that 50% of doses were taken with food and that the values of the oral clearance and volume of distribution depended upon whether a particular dose was taken with food or without food.

To mimic the actual drug administration protocol for food intake, we considered a different food effect in the abiraterone versus nilotinib trials. This was done to test whether the model would be able to capture two extreme food effects, the between-individual and between-occasion variability, and the individual level exposure. For abiraterone, patients in the fed prandial state were assumed to have had a high fat meal given the availability of Pop PK parameter values in the reference for simulation from this state; therefore, the oral clearance and volume of distribution were reduced by 92% and 85%, respectively, if the dose was taken with food [7]. In contrast to the abiraterone simulations, patients who were simulated as receiving nilotinib were assumed to have ingested a light fat meal and possibly just a glass of grape juice 2 hours before or 1 hour after nilotinib was taken. An 18% reduction in apparent clearance was introduced to reflect this food effect [9, 10].

Study Design

Patients in the simulated abiraterone trials were randomly assigned to take 1,000 mg once daily and patients in the simulated nilotinib trials were assigned to take a 300 or 400 mg tablet twice daily in 1:1 fashion. Virtual pharmacokinetic samples for each patient were assumed to occur at week 1, week 4, and month 2 and month 3 based on a previously established trial sampling schedule from a standard of care clinical follow up approach (see Figure 1) after the start of the trial so each individual had a total of 4 measurements (one sample obtained on each occasion). This sampling schedule was designed to fit in with the standard clinical follow up of the patient. Because the aim of the study was to simulate a trial similar to one in clinical practice, the samples were assumed to be withdrawn at random

time points during clinic hours. The visit day for each pharmacokinetic sample of each hypothetical patient was randomly selected from a discrete distribution with 50% of virtual patients having a visit sample drawn on the recommended day, 20% ± 1 day, 20% at ± 2 days and 10% at ± 3 days from the scheduled visit date. Each clinic visit time was randomly selected from a uniform distribution assuming regular office hours from 7am to 6pm. To mimic food intake when patients take their medications, a random food covariate was generated for each hypothetical patient and sampled for the four different clinic visit occasions within each patient.

The hypothetical patients were assigned into trial sizes of 20, 50 or 70 individuals, and each trial was replicated 100 times. The same study design was tested using three different between-occasion variability levels: 10, 25, and 40% CV on drug clearance.

Population Pharmacokinetic Parameter Estimation

The population pharmacokinetics of the hypothetical patients in each trial were analyzed using nonlinear mixed effect modeling software, NONMEM, Version VII (GloboMax_LLC, Ellicott City, MD, USA) using Wings for NONMEM, Version 7. One-compartment structural model with a proportional residual error model was tested using the first-order conditional estimation (FOCE) method. Between-individual variability was tested on oral clearance and volume of distribution, and between-occasion variability was tested on oral clearance only. The between-individual and between-occasion variability for Pop PK parameters were evaluated using an exponential model $P_{i,k} = P_{TV}\, x\, e^{\eta p,i}$ where $P_{i,k}$ is the parameter estimate for the i^{th} individual after the k^{th} dose administered and P_{TV} is the typical value for the parameter at the population level. The variability between the i^{th} individual and the population parameter value was described by $\eta_{p,i}$ which was assumed to be log-normally distributed with a mean of 0 and a variance of $\omega\eta\, p,i^2$ [11]. The variability between the k^{th} occasion of dose administration and the population parameter value was described by $\eta_{p,k}$ which was assumed to be log-normally distributed with a mean of 0 and a variance of $\omega_{\eta\, p,k}{}^2$. In addition to the between-individual and between-occasion variability, residual variability was described by a proportional error model. That is, $Y_{ij} = \hat{y}_{ij}(1+\varepsilon_{ij})$ where Y_{ij} and $\hat{Y}_{ij}$ are the j^{th} observed nilotinib or abiraterone concentration and its corresponding model predicted concentration, respectively, with the difference described by ε_{ij} which is assumed to be normally distributed with a mean of 0 and a variance of σ^2. In order to estimate between-occasion variability in the model, the residual error was fixed in the estimation step.

Evaluation of clinical trial designs

The food effect in each trial was evaluated by comparing the fit of a base model with no food effects with a model that includes a food effect covariate on oral clearance. The model comparison was based on a likelihood ratio test using the objective function value (OFV) from NONMEM. The change in the OFV returned by NONMEM is approximately equal to −2 × log likelihood. The difference in −2 × log likelihood between two models that are nested follows a χ^2 distribution. The significance level for identifying the food effect corresponded to a decrease in the OFV of greater than 6.63 (p-value≤ 0.01, df=1). The power to detect a food effect is the percent of the trials where the population PK analysis

demonstrated significant OFV change among the 100 trials in both abiraterone and nilotinib and retrieving a food effect value within 20% of the true food effect value.

In addition, to determining whether or not a food effect was detected by the trial design, the accuracy and precision of the model for retrieving parameter values of clearance, between-individual and between-occasion variability was assessed using two statistical standard criteria: percent bias and percent precision [12].

At the population level, the bias of each parameter represents the difference between the estimated values from the simulated (true) value of the population, and the percent bias is the mean predicted error normalized by the simulated value taken from the literature. The bias is calculated using the equation shown below:

$$\text{Population} \quad \% \quad \text{bias} = \frac{1}{m} \sum_{j=1}^{m} \frac{(Y_{p,j} - Y_e)}{Y_e} \times 100\%$$

where $Y_{p,J}$ is the predicted value for the j^{th} trial in total m trials with the same given between-occasion variability level and the same sample size, and Y_e is the literature value we simulated from. The precision was estimated by calculating the root mean square error, reflecting the distribution of variance, and the percent precision is the root mean square error normalized by the simulated mean. This included the bias and precision of the estimation of the food effect.

$$\text{Population} \quad \% \quad \text{precision} = \sqrt{\frac{\sum_{j=1}^{m} \left(\frac{Y_{p,j} - Y_e}{Y_e} \right)^2}{m}} \times 100\%$$

Parameter estimates at the individual level were evaluated using percent bias and percent precision.

$$\text{Individual} \quad \% \quad \text{bias} = \frac{1}{n} \sum_{i=1}^{n} \frac{(Y_{p,i} - Y_{e,i})}{Y_{e,i}} \times 100\%$$

where $Y_{p,i}$ and $Y_{e,i}$ are the predicted and simulated values for the i^{th} patient, respectively. n represents the number of patients in the trial.

$$\text{Individual} \quad \% \quad \text{precision} = \sqrt{\frac{\sum_{i=1}^{n} \left(\frac{Y_{p,i} - Y_{e,i}}{Y_{e,i}} \right)^2}{n}} \times 100\%$$

Then, an average of individual percent bias and precision of the m number of trials was calculated.

RESULTS

The percent bias and precision for the population oral clearance for abiraterone ranged from −37% to −31% and 36.2% to 38.1%, respectively (Table 3). The average percent bias and precision are noticeably smaller in magnitude for individual clearance estimates (range of 1.2% to 4.4% and 14.5% to 19.9%, respectively). This indicates that the model estimates for oral clearance are more accurate and less variable at the individual level compared to the population level. Across three between-occasion variability levels (10%, 25%, and 40%), 21%, 10% and 11% of the abiraterone trials, respectively, retrieved population clearance values within 20% of the true value. The ranges of percent bias and precision for between-individual variability were −45.1% to−42.1% and 42.8% to 46.1, respectively, with minimal variations with number of patients in the trial or between-occasion variability. The ranges of percent bias and precision of between-occasion variability were −30% to −1.11% and 11.6% to 40.7%, respectively (Table3). There was a decrease in both the between-occasion variability bias and precision as the number of patients and between-occasion variability increased. The known food effect on oral clearance for abiraterone was identified in 100% of simulated trials with 20, 50 and 70 patients for the 10%, 25%, and 40% between-occasion variability levels. The ranges of percent bias and precision of food effect were 2.01% to 4.42% and 6.81% to 14.4%, respectively.

The percent bias and precision on the population oral clearance for nilotinib ranged from −13.3% to −11.8% and 14.2% to17.0%, respectively (Table 4) and were consistent across between-occasion variability levels (10%, 25% and 40%). In contrast to abiraterone, the average individual nilotinib oral clearance estimates were significantly more accurate and precise than population estimates with the percent bias and precision ranging from −1.9% to −0.5% and 4.2% to 8.6%, respectively. Across three between-occasion variability levels (10%, 25% and 40%), 86%, 84% and 83% of the nilotinib trials, respectively, retrieved the population oral clearance within 20% of the true value. The ranges of percent bias and precision of between-individual variability were −9.9% to −7. 9% and 11.3% to 19.4%, respectively and ranged from −3.9% to −0.4% and 4.9% to 11.0% for percent bias and precision on between-occasion variability. Retrieval of the known food effect in this system was observed in 100% of the simulated nilotinib trials with 10% between-occasion variability with trial sizes of 25, 50, and 70 patients. For nilotinib trials simulated with 25% between-occasion variability, significant food effects on oral clearance were retrieved in 80% of 20 patient trials, 99% of 50 patient trials, and 100% of 70 patient trials. Nilotinib trials simulated with 40% between-occasion variability resulted in significant food effects on clearance being retrieved in 50% of 20 patient trials, 78% of 50 patient trials, and 88% of 70 patient trials. The ranges of percent bias and precision of food effect were - 2.16% to 11.8% and 6.3% to 38.8%, respectively.

DISCUSSION

Virtual clinical trials of abiraterone and nilotinib using sparse concentration measurements and a population PK sampling time design were simulated to test whether the drug exposure of each simulated patient and its variability under different prandial conditions on oral clearance for two recently approved drugs would be retrieved accurately and precisely. The

trial design is a typical phase II design in the NCI cooperative system and this assessment provides and evaluates whether there is value in drawing sparse samples to utilize in population pharmacokinetic analysis for the determination of individual drug exposure. It was important to assess this particular study design as it is widely used and insight on the value of drug concentration sampling under these conditions was unclear. Population as well as individual pharmacokinetic parameters for abiraterone, with a large food effect, and nilotinib, with a smaller food effect, were well estimated from the virtual trial results. This evaluation of whether between-individual and between-occasion variability can be well captured with a significant covariate effect on oral clearance (the underlying food effect) at different levels of variability on anticancer drug exposure is a novel observation. As the prior knowledge of more than 100% between-individual variability was introduced to oral clearance in the abiraterone trial, the model estimation of the population oral clearance parameter and between-individual variability have relatively poor percent bias and precision compared to the nilotinib trial. This is reflected in the power calculation showing that only 10 to 20% of the trials across three between-occasion variability levels (10, 25, 40%) have population oral clearance estimates within 20% of the true value. This finding indicates that retrieving population level effects with large between-individual variability may need a much larger trial size or more intense sampling schedule or a combination of both.

Between-occasion variability estimates were reasonable considering both percent bias and precision were less than 30% in most trial simulations. However, the percent bias and precision were relatively poor for the simulated abiraterone trials with 20 patients and 10% within-individual variability. One possible explanation of this is that the system is less able to capture between-individual variability if the actual variability is small, but the true mechanism contributing to this poor bias at 10% between-individual variability is as yet unclear.

This model was unable to accurately estimate both residual error and between-occasion variability simultaneously. In order to accurately capture the between-individual variability, the residual error estimation was fixed to published values. This suggests that more than one sample per occasion will be required to distinguish these hierarchies of variability simultaneously.

The effects of two important features of such clinical trials were quantified using a NONMEM based simulation analysis. These were the power to detect differences in oral drug clearance related to the prandial state of the study participants and the degree of between-individual variability and sample size. When the between-individual variability was set to 25% for a trial with 20 patients, 80% of the simulated nilotonib trials resulted in the detection of a statistically significant reduction in oral clearance caused by the food effect. The power to detect this food effect on oral drug clearance increased to 100% when the number of patients per trial was increased from 20 to 70. At 40% between-individual variability, the food effect signal was observed in only 50% of trials with 20 patients, increasing to 88% when the number of patients increased to 50. The percent precision also indicated that the food effect as a covariate was captured less precisely when between-occasion variability increased, and the trial sample size was reduced. In contrast, abiraterone with a much more substantial food effect (92% reduction in oral clearance) resulted in a

power to detect the food effect of 100% in the smallest trial evaluated (20 patients). This virtual trial also had 40% between-individual variability and resulted percent bias and precision on the Pop PK parameters that were all less than 20%. Using a modeling approach, we were able to simulate a complex clinical oncology population pharmacokinetic trial setting and capture the between-occasion variability and the magnitude of individual drug exposure in the presence of a large food effect for two recently approved oral anti-cancer agents. This simulated approach facilitated an early evaluation of the proposed trial design. However, clinical trial simulations are generated based on many trial assumptions, and these assumptions may include uncertainty. In fact, with different underlying assumptions, the simulated outcomes can differ, so multiple scenarios as well as assumptions must be tested in order to fully interpret the relevance of the results.

There are limitations to this analysis. First, a dropout model was not incorporated in this study design which can potentially contribute to censor events in a 3 month study. The simulations also assumed parameter distributions based on available food effect assessment in previous non-compartmental analysis. Because of the established sampling schedule, both drugs were better estimated with a simplified model structure. Despite this, the model provides an approximation of the actual behavior and can capture the trend of the variability within the population. In fact, this simplified modeling approach was previously proposed to assess the pharmacokinetics of some drug entities in the trials with a relative sparse sampling schedule [13-14]. The sampling schedule could also be optimized for the identification of food effects and model parameters, but the objective of this work was to evaluate pharmacokinetics and food effect given a commonly used sampling schedule. Second, non-compliance was not considered in this study design as we assumed that the compliance rate should be reasonably controlled in the clinical trial although this will result in a higher residual error and between-individual variability than compliance accounted for using electronically monitoring [15].

This study emphasizes the importance of addressing trial designs where intensive sampling cannot be obtained and yet there is a need to understand the drug exposure characteristics to what are otherwise medications with highly variable pharmacokinetic disposition.

ACKNOLEDGEMENTS

Robert R.Bies had support through the Indiana Clinical Translational Sciences Institute from a gift of Eli Lilly and Company and Cancer and Leukemia Group B for the submitted work. Lionel D. Lewis was supported in part by CA 023108 in the previous 3 years. Claire H. Li and Eric A. Sherer declare no conflict of interests. There are no other author relationships or activities that could appear to have influenced the submitted paper. We appreciate the valuable comments from Dr. Mark J. Ratain.

ABBREVIATIONS

PK	pharmacokinetic
POP PK	population pharmacokinetic
CL	oral clearance
V	apparent oral volume of distribution

CV	coefficient of variation
FOCE	first-order conditional estimation
OFV	objective function value

REFERENCES

1. McLeod HL, Evans WE. Oral cancer chemotherapy: the promise and the pitfalls. Clin Cancer Res. 1999; 5:2669–2671. [PubMed: 10537326]
2. Martinez MN, Amidon GL. A mechanistic approach to understanding the factors affecting drug absorption: A review of fundamentals. J Clin Pharmacol. 2002; 42:620–643. [PubMed: 12043951]
3. Winstanley PA, Orme ML. The effects of food on drug bioavailability. Br J clin Pharmac. 1989; 28:621–628.
4. Gu CH, Li H, Levons J, Lentz K, Gandhi RB, Raghavan K, Smith RL. Predicting effect of food on extent of drug absorption based on physicochemical properties. Pharmaceutical Research. 2007; 24:1118–1130. [PubMed: 17385020]
5. Koch KM, Reddy NJ, Cohen RB, Lewis NL, Whitehead B, Mackay K, Stead A, Beelen AP, Lewis LD. Effects of food on the relative bioavailability of lapatinib in cancer patients. J Clin Oncol. 2009; 27:1191–1196. [PubMed: 19188677]
6. Kang SP, Ratain MJ. Inconsistent labeling of food effect for oral agents across Therapeutic Areas: Differences between Oncology and Non Oncology Products. Clin Cancer Res. 2010; 16:4446–4451. [PubMed: 20736327]
7. Ryan CJ, Smith MR, Fong L, Rosenberg JE, Kantoff P, Raynaud F, Martins V, Lee G, Kheoh T, Kim J, Molina A, Small EJ. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol. 2010; 28:1481–1488. [PubMed: 20159824]
8. ZYTIGA label. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2011/202379lbl.pdf
9. Tanaka C, Yin OQ, Sethuraman V, Smith T, Wang X, Grouss K, Kantarjian H, Giles F, Ottmann OG, Galitz L, Schran H. Clinical pharmacokinetics of the BCR-ABL tyrosine kinase inhibitor nilotinib. Clin Pharmacol Ther. 2010; 87:197–203. [PubMed: 19924121]
10. Yin OQ, Gallagher N, Li A, Zhou W, Harrell R, Schran H. Effect of grapefruit juice on the pharmacokinetics of nilotinib in healthy participants. J Clin Pharmacol. 2010; 50:188–19. [PubMed: 19948946]
11. Feng Y, Pollock BG, Ferrell RE, Kimak MA, Reynolds CF 3rd, Bies RR. Paroxetine: population pharmacokinetic analysis in late-life depression using sparse concentration sampling. Br J Clin Pharmacol. 2006; 61:558–569. [PubMed: 16669849]
12. Huang J, Jacobson P, Brundage R. Prediction of unbound mycophenolic acid concentrations in patients after hematopoietic cell transplantation. Therapeutic Drug Monitoring. 2007; 29:385–390. [PubMed: 17667790]
13. Scerwin CM, Saldaña SN, Bies RR, Aman MG, Vinks AA. Population pharmacokinetic modeling of risperidone and 9-hydroxyrisperidone to estimate CYP2D6 subpopulations in children and adolescents. Ther Drug Monit. 2012; 34(5):535–544. [PubMed: 22929407]
14. van Erp NP, Baker SD, Zandvliet AS, Ploeger BA, den Hollander M, Chen Z, den Hartigh J, König-Quartel JM, Guchelaar HJ, Gelderblom H. Marginal increase of sunitinib exposure by grapefruit juice. Cancer Chemother Pharmacol. 2011; 67(3):695–703. [PubMed: 20512335]
15. Vrijens B, Tousset E, Rode R, Bertz R, Mayer S, Urquhart J. Successful projection of the time course of drug concentration in plasma during a 1-year period from electronically compiled dosing-time data used as input to individually parameterized pharmacokinetic models. J Clin Pharmcol. 2005; 45(4):461–467.

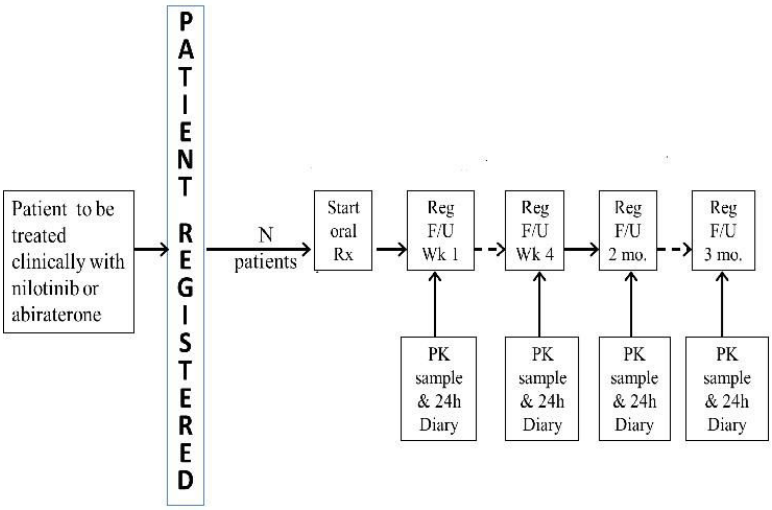

Figure 1.
Study schema of abiraterone and nilotinib clinical trials.

Table 1

Population pharmacokinetic parameters for abiraterone patients

Abiraterone		
Parameter	**Fasting status Mean (SD)**	**Fed status Mean (SD)**
Apparent Clearance / bioavailability [CL/F] (L/h)	2650 (4617)	231 (97.7)
Apparent Volume of distribution / bioavailability [Vd/F] (L)	25494 (18670)	4069 (1462)
Absorption rate (1/h)	1.65 (0.33)	1.65 (0.33)

F = oral bioavailability

Absorption rate is fixed to be 1.65 1/h with standard deviation of 0.33.1/h.

Table 2

Population pharmacokinetic parameters for nilotinib patients

Nilotinib		
Parameter	**Fasting status Mean (SD)**	**Fed status Mean (SD)**
Apparent Clearance / bioavailability [CL/F](L/h)	33 (18)	27(15)
Apparent Volume of distribution / bioavailability [Vd/F] (L)	720 (267)	604(181)
Absorption rate (1/h)	0.74 (0.15)	0.74 (0.15)

F = oral bioavailability

Absorption rate is fixed to be 0.74 1/h with standard deviation of 0.15 1/h.

Table 3

Bias and precision of abiraterone oral clearance at the population level and individual level, between-individual variability, and between-occasion variability

Between-occasion variability	Number of patients in trial	Oral Clearance – Population level		Oral Clearance – Individual level		Between-individual variability		Between-occasion variability		Food effect	
		Bias	Precision	Bias	Precision	Bias	Precision	Bias	Precision	Bias	Precision
10%	20	−32.3%	37.1%	1.5%	14.5%	−44%	45.6%	−30%	40.7%	2.65%	9.95%
	50	−36.6%	37.8%	1.3%	14.6%	−43.6%	44.5%	−25.8%	30.8%	4.42%	7.42%
	70	−36.8%	37.8%	1.4%	14.9%	−43.3%	43.5%	−15.3%	23.3%	3.84%	6.81%
25%	20	−31.7%	36.6%	3.3%	19.6%	−45.1%	45.9%	−5.85%	18.8%	2.36%	11.8%
	50	−36.3%	37.6%	1.2%	18.9%	−42.4%	42.8%	−5.51%	14.6%	4.16%	8%
	70	−36.9%	37.9%	3.2%	19.9%	−43 %	43%	−3.08%	14.8%	3.61%	7.22%
40%	20	−31%	36.2%	1.4%	19.7%	−44.9%	46.1%	−1.34%	17.4%	2.01%	14.4%
	50	−35.7%	37.1%	1.6%	19.9%	−42.1%	42.8%	−1.44%	13.4%	2.52%	11.9%
	70	−37%	38.1%	4.4%	19.6%	−42.6%	43%	−1.11%	11.6%	2.64%	8.6%

Table 4

Bias and precision of nilotinib oral clearance at the population level and individual level, between-individual variability, and between-occasion variability

Between-occasion variability	Number of patients in trial	Oral Clearance – Population level		Oral Clearance – Individual level		Between-individual variability		Between-occasion variability		Food effect	
		Bias	Precision	Bias	Precision	Bias	Precision	Bias	Precision	Bias	Precision
10%	20	−11.8%	16.0%	−0.6%	4.6%	−9.0%	18.1%	−3.9%	11.0%	−0.12%	12.3%
	50	−12.0%	16.3%	−0.5%	4.3%	−9.9%	13.4%	−2.1%	6.9%	−0.05%	12.3%
	70	−12.8%	14.2%	−0.5%	4.2%	−8.0%	11.3%	−2.3%	5.7%	−0.04%	6.3%
25%	20	−12.0%	16.2%	−1.5%	6.6%	−8.8%	18.5%	−1.9%	8.9%	−0.4%	30%
	50	−12.4%	16.7%	−1.0%	6%	−9.1%	13.1%	−1.2%	5.2%	0.9%	20.9%
	70	−13.3%	14.7%	−0.8%	5.7%	−7.9%	11.7%	−0.9%	4.9%	−1.39%	15.5%
40%	20	−12%	16.4%	−1.9%	8.6%	−8.5%	19.4%	−1.8%	8.7%	11.8%	38.8%
	50	−12.7%	17.0%	−1.0%	7.2%	−9.2%	13.9%	−0.4%	7.7%	2.32%	30%
	70	−13.3%	14.7%	−0.9%	7.1%	−7.9%	12.3%	−0.7%	4.9%	−2.16%	24.3%